Kaohsiung Journal of Medical Sciences (2016) 32, 391–396

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REVIEW ARTICLE

Therapeutic potential of melatonin in oral medicine and periodontology

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Received 21 April 2016; accepted 23 June 2016
Available online 25 July 2016

KEYWORDS
Antioxidants;
Melatonin;
Oral cancer;
Osseointegration;
Periodontitis

Abstract Melatonin (*N*-acetyl-5-methoxy tryptamine) is a substance secreted by multiple organs in vertebrates. In addition to playing a part in the circadian cycle of the body, melatonin is known to have antioxidant, antiinflammatory, and antioncotic effects on human tissues. Oral cavity is affected by a number of conditions such as periodontitis, mucositis, cancers, and cytotoxicity from various drugs or biomaterials. Research has suggested that melatonin is effective in treating the aforementioned pathologies. Furthermore, melatonin has been observed to enhance osseointegration and bone regeneration. The aim of this review is to critically analyze and summarize the research focusing on the potential of melatonin in the field of oral medicine. Topical administration of melatonin has a positive effect on periodontal health and osseointegration. Furthermore, melatonin is particularly effective in improving the periodontal parameters of diabetic patients with periodontitis. Melatonin exerts a regenerative effect on periodontal bone and may be incorporated into of periodontal scaffolds. The cytotoxic effect of various drugs and dental materials may be countered by the antioxidant properties of melatonin. Topical administration of melatonin promotes the healing of tooth extraction sockets and may also impede the progression of oral cancer. Although, there are a number of current and potential applications of melatonin, further long term clinical and animal

Conflicts of interest: All authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.kjms.2016.06.005

studies are needed to assess its efficacy. Moreover, the role of melatonin supplements in the management of periodontitis should also be assessed.

Introduction

Melatonin (*N*-acetyl-5-methoxy tryptamine) is a substance secreted by multiple organs including the pineal gland, retina, bone marrow, the gastro-intestinal track, and the immune system. Its main function is the regulation of the circadian rhythm (day—night cycles) [1]. It plays an anti-inflammatory, antioncotic, and immunomodulatory role by scavenging free-radicals and via interactions with cell membrane and intracellular proteins [2]. The chemical structure of melatonin is shown in Figure 1.

Melatonin is capable of entering the oral cavity by diffusing into the saliva from blood. As the majority of the melatonin remains bound to serum albumin, the amount of melatonin in saliva is approximately one third of that present in the blood [3]. Melatonin mainly exerts antioxidant effects by interacting with melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) receptors on cells [4,5]. Perhaps, a potent antiinflammatory property of melatonin is linked to its ability to act as a scavenger of exogenous and endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) [6]. In addition, both ROS and RNS have been associated with DNA mutations leading to carcinogenesis [7]. The existence of MT1 receptors on healthy and cancerous oral mucosal cells is suggestive that melatonin may act as an antiinflammatory or antioncotic agent in the oral cavity [8]; for example, its antiinflammatory effects have been reported on human gingival fibroblasts [9]. Furthermore, intraperitoneal melatonin has been reported to reduce periodontitis in diabetic rats [10]. Similarly, topical application of melatonin in diabetic patients has diminished the progression of periodontal bone loss as evident by the down-regulation of proinflammatory factors [11—13]. Hence, it has been suggested that melatonin may be used in the management of periodontitis and antioncotic agents for oral cancer cells [8,14,15]. The aim of this review is to critically analyze and summarize the research focusing on the potential of melatonin in the fields of oral medicine and periodontology.

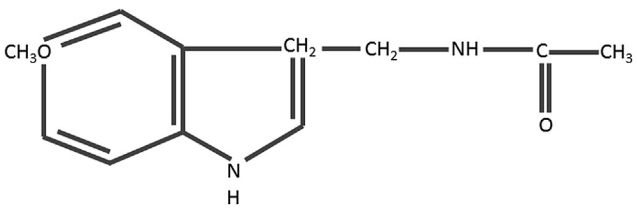

Figure 1. Chemical structure of melatonin (*N*-acetyl-5-methoxy tryptamine).

Melatonin for the treatment of periodontitis

Periodontitis results in progressive destruction of tooth supporting tissues (cementum, periodontal ligament, and alveolar bone) and subsequently loss of teeth. In spite of various surgical and nonsurgical therapeutic options, the global prevalence of periodontitis is still remarkably high (40—90%) [16]. In addition to *in vitro* studies [9], animal studies and clinical trials have documented the therapeutic effects of melatonin on periodontitis (Table 1).

Local and systemic administration of melatonin in rats with lipopolysaccharide-induced periodontitis reduced the level of enzymes (such as serum aspartate aminotransferase, alanine transaminase, and blood urea nitrogen) significantly compared with rats in the control group [17,18]. Similarly, locally administered melatonin significantly reduced bone resorption compared with rats receiving no treatment. These studies suggested that topical administration of melatonin can be used as an adjunct to conventional treatment protocols such as scaling, root planing, and surgical debridement to improve the outcomes of periodontal therapy.

As diabetes mellitus has a two-way relationship with periodontal diseases [19], melatonin has been used for therpeutic applications for cases of diabetes-induced perdiontitis. It has been reported that administration of melatonin reduced osteoclast activity and alveolar bone loss in the diabetic rats with periodontitis melatonin [20]. In addition, diminished oxidative stress index and reduced alveolar bone loss have been observed in similar diabetic animal models [10]. The effects of melatonin on diabetic patients appear twofold: (1) the inherent antiinflammatory and antioxidant properties of melatonin reduce the magnitude of inflammation in the periodontal tissues [2]; and (2) melatonin scavenges the ROS produced due to diabetes and, therefore, reduces the inflammatory effects of diabetes on the periodontium [21].

Melatonin not only down-regulates the expression of proinflammatory factors such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha [11], but it also down-regulates receptor activators of nuclear factor kappa-B ligand/osteoprotegerin ratios to reduce periodontal inflammation [11—13]. In addition to up-regulation of salivary acid phosphatase, alkaline phosphatase, osteopontin, and osteocalcin, it results in significant improvements in gingival index and pocket depth. These facts are indicative of enhanced osteoblast differentiation and bone formation following topical administration of melatonin [12]. However, further well-designed studies with longer follow-up periods are needed to ascertain the long-term efficacy of melatonin in treating periodontitis in the clinical settings.

Table 1 A summary of clinical studies conducted on the treatment of diabetes-induced with topical 1% metformin.

Study & y	Patients (*n*)	Mean age of patients	Methodology	Treatment groups		Follow-up	Conclusion
				Control (healthy)	Test (DM + periodontitis)		
Cutando et al. 2013 [12]	60	47	Assessment of PD and GI; salivary concentration of acid and alkaline phosphatase, osteopontin and osteocalcin	Orabase/d	1% MT + Orabase/d	20 d	1% MT + Orabase improved periodontal parameters and reduced phosphatase, osteopontin and osteocalcin levels in diabetic patients.
Cutando et al. 2014 [13]	60	47	Assessment of PD and GI; salivary concentrations of RANKL and OPG	Orabase/d	1% MT + Orabase/d	20 d	1% MT + Orabase improved periodontal parameters and reduced RANKL/OPG ratio in diabetic patients
Cutando et al. 2015 [11]	60	47	Assessment of PD and GI; salivary concentrations of CRP, IL-6 and TNF-α	Orabase/d	1% MT + Orabase/d	20 d	1% MT + Orabase improved periodontal parameters and reduced CRP, IL-6 and TNF-α levels in diabetic patients.

CRP = C-reactive protein; DM = diabetes mellitus; GI = gingival index; IL-6 = interleukin-6; MT = melatonin; OPG = osteoprotegerin; PD = pocket depth; RANKL = receptor activators of nuclear factor kappa-B ligand; TNF- α =, tumor necrosis factor-alpha.

Melatonin and osseointegration of dental implants

Dental implants require surface modifications in order to increase their bioactivity prior to their placement in periodontal bone [22,23]. However, there are several drawbacks of modified implants such as delamination of the bioactive coating, ion leakage, and particle residues [23]. Melatonin has the potential to act as a viable alternative to unstable implant coatings. Administration of powdered melatonin to implant sites resulted in significantly higher interthread bone formation and bone mineralization in experimental dogs compared with control implant sites [24]. Melatonin augments the osteogenic effects of porcine bone grafts on calcium-coated titanium dental implants placed in experimental dogs [25]. Moreover, combination with growth hormone seems to augment the effects of melatonin on implant sites *in vivo* [26]. Intraperitoneal injections of melatonin combined with fibroblast growth factor-2 (FGF-2) around titanium and zirconia implants have been observed to promote a greater bone—implant contact [27,28]. Results obtained in a 3-month clinical trial suggest that melatonin may prove to be clinically effective to enhance the osseointegration of dental implants [29]. Nevertheless, more long-term animal and human studies are indeed required to further explore the osteoconductive effect of melatonin on implants.

Melatonin for countering the cytotoxicity of drugs and dental materials

A number of drugs are known to affect the periodontium. Proksch et al. [30], reported that melatonin reduced the levels of reactive oxidative species and cytotoxic effects of commonly used oral antiseptic medicaments (e.g., chlorhexidine). Melatonin also plays a protective role against the necrotic effects of bisphosphonates on periodontal cells [31]. Therefore, topical application of melatonin prior to dental surgery may prevent bisphosphonate-related osteonecrosis of the jaws. Methacrylate compounds present in commonly used dental polymers are known to have cytotoxic effects [32]. Due to antioxidant properties, melatonin has been observed to protect dental pulp cells against DNA damage due to methacrylate [33]. Therefore, melatonin, in the form of sublingual tablets, gels, or mouth rinses has the potential to inhibit the genotoxic effects of methacrylate-based dental materials.

Application of melatonin in postextraction tooth sockets

Tooth extraction is a traumatic surgical procedure. Production of ROS and RNS contributes to manifestation of inflammation and/or infection at the site of extraction [6,34]. Indeed, placement of melatonin in the extraction sockets of dogs normalizes the levels of lipid peroxides, nitrates, and nitrites raised in reaction to tooth extraction [35]. By contrast, a clinical study conducted on 10 patients failed to replicate the effects of melatonin observed in animal studies [36]. Therefore, efficacy of applying topical melatonin on postextraction sockets is debatable and more

research is required to assess its potential for clinical applications.

Effect of melatonin on bone regeneration

As discussed earlier, melatonin is known to stimulate the proliferation of osteoblasts and promote bone formation [37]. Additionally, the immunomodulatory, antioxidant, and antiinflammatory effects may further add to the osteoconductive effects of melatonin [38,39]. Bioactive scaffolds and bone grafting materials are used to induce regeneration of bone which has been lost due to periodontal disease or tooth loss [40]. It has been observed that calcium aluminate scaffolds, containing melatonin and platelet-rich plasma have a proliferative effect on human osteoblasts [41]. Melatonin-based scaffold hold a promising outcome in guided tissue regeneration applications in the future.

Effect of melatonin on oral cancer

As ROS are involved in the manifestation of precancerous lesions such as leukoplakia and lichen planus [42,43], melatonin plays a preventative or therapeutic role against oral cancer due to its antioxidant properties. Additionally, melatonin prevents damage to healthy tissues due to radiotherapy, which is routinely employed to treat oral cancers [44]. A recent *in vitro* study suggests that melatonin may impede metastasis of oral cancer by inhibiting metalloproteinase-9 activation [45]. Therefore, oral rinses, gels, and toothpastes containing melatonin may be beneficial for impeding and preventing oral cancer.

Melatonin as an antimicrobial agent

Melatonin possesses antimicrobial properties against a variety of bacteria and viruses [46,47]. However, to the authors' best knowledge, no studies have been conducted testing the effects of melatonin against cariogenic bacteria such as *Staphylococcus mutans* and *Lactobacillus*. Nevertheless, in 1976, a study by Mechin and Toury [48] reported significantly reduced caries in rats receiving intraperitoneal injections of melatonin compared with those receiving no melatonin injections. The direct antimicrobial action of melatonin, synergistically supported by its immunomodulatory and antioxidant properties may prove to be a potent weapon against numerous oral infections.

Limitations of melatonin in oral medicine and periodontology

In spite of various studies suggesting a potential of melatonin in various fields of dentistry, there are some limitations that should be overcome. Although the positive impact of melatonin on general health has been suggested [49], no studies have attempted to analyze the impact of increased intake of melatonin-rich foods such as grapes, bananas, herbs, rice, and cereals on the periodontal health or periodontal treatment. Food and Drug Association has approved melatonin as a supplement for the treatment of insomnia and sleep-disorders [50]. However, to date, no studies have evaluated the impact of dietary melatonin supplements on periodontal parameters. Studies should be conducted to observe the effect of using systemic melatonin alongside conventional nonsurgical and surgical therapy to assess its feasibility as a long-term therapeutic agent for the management of periodontitis. Well-designed, multicenter studies should be conducted before melatonin may be accepted in routine dental practice. Additionally, there is a lack of research focusing on the effect of melatonin on the growth of periodontal and peri-implant microflora. Therefore, generally speaking, more studies are needed to construe a safe and effective dose of melatonin in oral medicine.

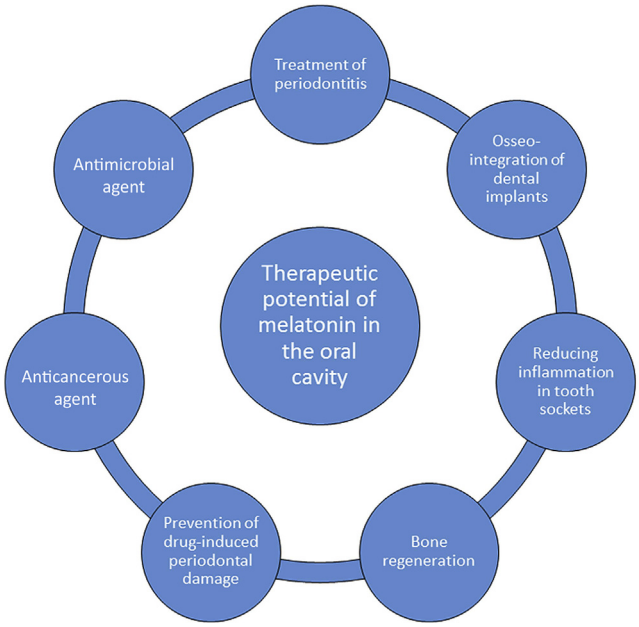

Figure 2. Therapeutic potential of melatonin in oral medicine and periodontology.

In conclusion, a number of positive effects of melatonin on the periodontium and its potential therapeutic roles have been documented in literature (see Figure 2). Melatonin shows promise in the management of diabetes-associated periodontitis, periodontal regeneration, oral implantology, and preventative dentistry. However, more clinical as well as animal studies are required to ascertain the use of melatonin in the clinical setting.

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